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TITLE: Guided Interventions for Prostate Cancer Using 3D-Transurethral Ultrasound and MRI Fusion

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Gland-sparing procedures that target specific areas of the prostate have been reported, using laser and HIFU techniques. These focal therapies require real-time visualization of the prostate during intervention, which is cumbersome to perform while the patient is in an MRI. Magnetic Resonance-Ultrasound (MR-US) fusion allows for specific targeting of the tumors in real-time during clinical interventions, outside of an MR suite. However, existing MR-US fusion exclusively utilizes TRUS. By utilizing a circumferentially wrapped catheter-based transducer, the entire prostate may be visualized at once; improving image registration and reducing motion errors. 3D TUUS imaging has been demonstrated in a phantom setting illustrating that the entire prostate gland can be visualized at once. This imaging advance may serve as a platform technology allowing the development of image guided focal prostate therapy.

15. SUBJECT TERMS
Ultrasound, prostate cancer, transurethral, MRI, image fusion

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1. **Introduction:**
   Curative therapies for prostate cancer (CaP) include surgical resection, irradiation, or ablation of the entire gland. Focal or site-specific treatment of CaP, while still early in investigation, requires an accurate real-time visualization of the prostate. An increasing body of literature documents the advantages of Magnetic Resonance-Ultrasound fusion for targeting specific tumors within the prostate. However, these approaches rely on transrectal ultrasound (TRUS), which suffers from registration and motion artifacts, as well as poor visualization of the anterior prostate. It is proposed that the use of a catheter-based transurethral ultrasound (TUUS) device has the ability to image the prostate in 3D with higher resolutions than TRUS. The overall objective of this proposal is to validate and clinically evaluate the use of 3D-TUUS in men undergoing needle-based interventions of the prostate. MR imaging will be used as the gold standard to compare TUUS and TRUS images. Achieving this goal will be facilitated by an FDA-approved radially-phased intravascular ultrasound device (Visions, Volcano Therapeutics), which will be clinically tested for use in the prostate.

2. **Keywords:**
   Ultrasound, MRI, image fusion, prostate cancer, transurethral
3. **Accomplishments:**
   a. **Major Goals of the Project**
      i. **Training and education development in prostate cancer research**
      ii. **Validate and refine 3D reconstruction accuracy of TUUS imaging**

Major Task 1: Training and educational development in prostate cancer research *(only applicable to training award mechanisms)*	**Months**	**UCLA**
Subtask 1: ARC Training and Certification Program	1-6	In Progress
Subtask 2: Biweekly progress update meeting with mentor	1-24	Dr. Grundfest
Subtask 3: Biweekly meeting with co-mentor	1-24	Dr. Marks
Subtask 4: IRB Training	1-24	Completed
Subtask 5: Attend Urology Grand Rounds Weekly Conferences	1-24	In Progress
Milestone(s) Achieved: Presentation of project results at a conference	24	

Research-Specific Tasks:

Specific Aim 1: Validate and refine 3D reconstruction accuracy of TUUS imaging		**UCLA**
Subtask 1: Validation of the image reconstruction accuracy of	1-3	In Progress

MR and TUUS in phantoms		
Subtask 2: Compare volume reconstruction accuracy to 3D TRUS	4-12	In Progress
Milestone(s) Achieved: Validation of 3D TUUS reconstruction accuracy	12	In Progress
Specific Aim 2: Validate MR-TUUS image registration error	10-21	UCLA
Milestone(s) Achieved: Validation of MR-TUUS image registration error with MRI and compared to 3D TRUS	21	
Specific Aim 3: Pilot study to evaluate MR-TUUS fusion in brachytherapy needle placement	13-24	UCLA
Major Task 1: Develop planning software to track needle insertion		
Major Task 2: Determine error in needle placement		
Milestone(s) Achieved: Assessed the use of TUUS in needle guidance in brachytherapy	24	

b. **Accomplished Goals**
   i. **Implemented TUUS prostate phantoms**
   ii. **Imaged TUUS prostate phantoms**
   iii. **Submitted an IRB for pilot study**

During the reporting period of (29 September 2014 – 28 September 2015) biweekly progress report meetings with my mentor Dr. Grundfest and co-mentor Dr. Marks were done. IRB training was completed, ARC training is in progress and urology grand rounds weekly conferences have been attended. Research was conducted toward the aim of validating and refining 3D reconstruction accuracy of transurethral ultrasound (TUUS) imaging. To work towards accomplishing

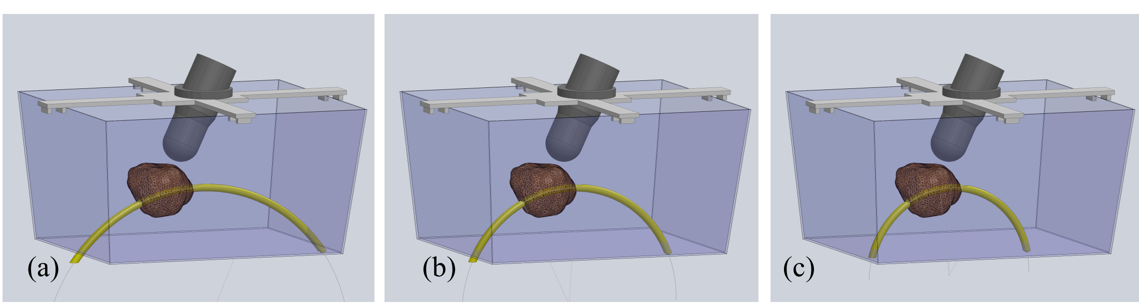

Figure 1: SOLIDWORKS CAD software prostate phantom model, (a) with 20 deg urethra bend, (b) 30 deg urethra bend, and (c) 40 deg urethra bend.

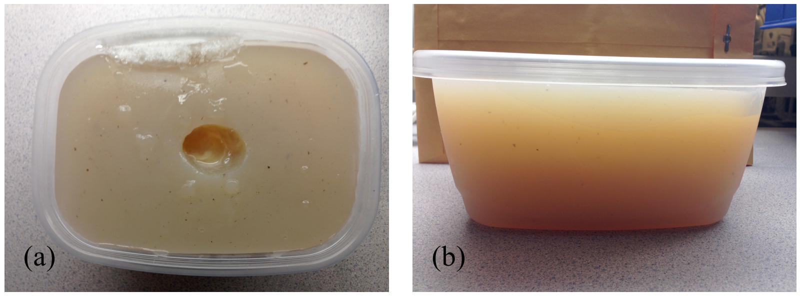

Figure 2: Prostate phantom for TUUS, TRUS, and MRI imaging.
(a) top view, (b) side view.

this goal three TUUS prostate phantoms with three prostatic urethra bend of 20 degrees, 30 degrees and 40 degrees were designed in SOLIDWORKS CAD software to develop a prostate phantom model (**Fig. 1**). The prostate is the same shape and size in all three images in Fig. 1, only the prostatic urethra bend is different. This was done to see the effect of the prostatic bend on TUUS imaging. These three angles of curvature were chosen around the mean prostatic urethra bend of 29.0 degrees with a standard deviation of 12.2 degrees [i]. The phantoms

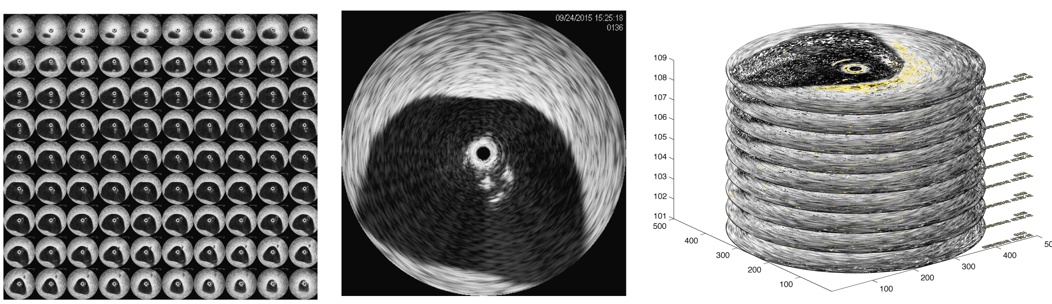

Figure 3: TUUS ultrasound images of prostate phantom with 20 deg urethra bend, (left) montage of prostate, (middle) slice of the middle of prostate, (right) 3D stack of prostate.

were designed for imaging with standard transrectal ultrasound (TRUS) probe, a TUUS probe, and MRI.

The TUUS phantoms were prepared using a standard recipe [ii] for the prostate and the 3D printed mold designed in SOLIDWORKS. Figure 2 illustrates an example of the TUUS phantom after fabrication. An FDA approved radially-phased 64-element array intravascular ultrasound (IVUS) device (Visions, Volcano Therapeutics) 8.2 French catheter and Volcano s5 imaging system were used for the TUUS imaging.

The IVUS was electronically controlled to yield 2D images that were stitched to reconstruct a high quality 3D image of the prostate. TRUS imaging was accomplished using a Hitachi Hi-Vision 5500 Ultrasound system with 7.5 MHz end-fire endorectal probe. 3D TRUS acquisition utilized an FDA-approved targeting and tracking system for prostate biopsy (Artemis, Eigen, Grass Valley, CA). This device employs digital video processing of conventional ultrasound images, which allows it to create a contemporaneous 3D reconstruction of the

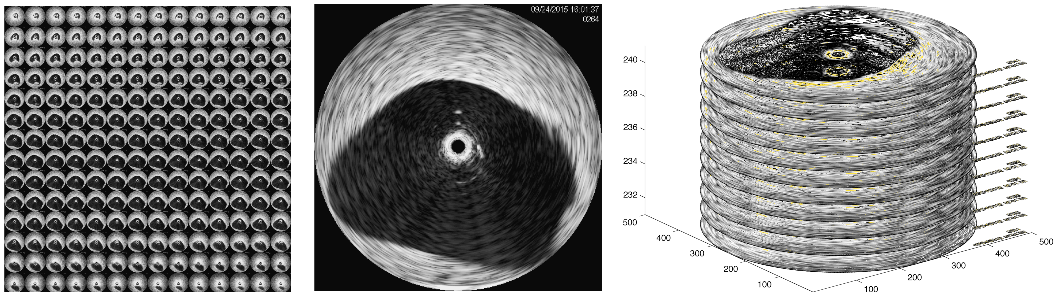

Figure 4: TUUS ultrasound images of prostate phantom with 30 deg urethra bend, (left) montage of prostate, (middle) slice of the middle of prostate, (right) 3D stack of prostate.

prostate and digitally record and store the biopsy sites for serial study and sampling.

All three phantoms were imaged using the TUUS probe and the 3D TRUS probe and system. MRI imaging was not accomplished due to the current lack of physical access to the machine and personal to operate the machine. I have made

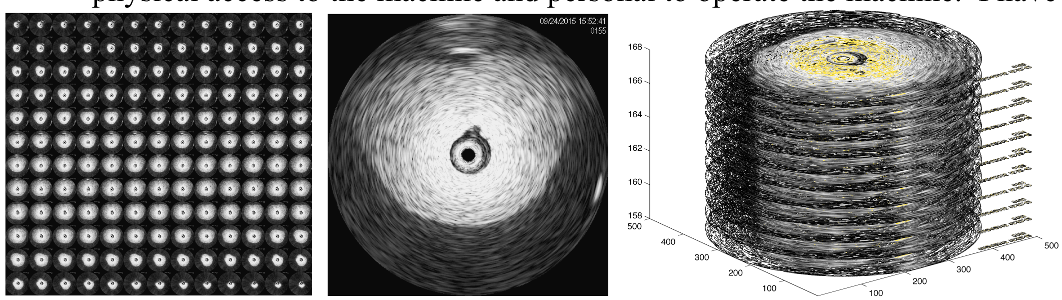

Figure 5: TUUS ultrasound images of prostate phantom with 40 deg urethra bend, (left) montage of prostate, (middle) slice of the middle of prostate, (right) 3D stack of prostate.

contact with the appropriate staff members that will help with getting after hours access to the MR machine. MR imaging of all three prostate phantoms is planned for the next month. A montage, a slice and 3D image stack of the TUUS prostate

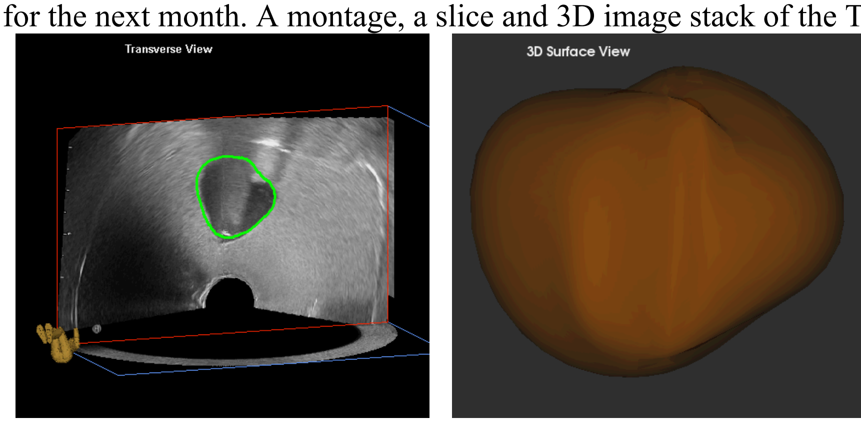

Figure 6: TRUS ultrasound images of prostate phantom with 20 deg urethra bend, (left) 2D prostate image, (right) 3D volume of prostate phantom.

image with the 20 degree, 30 degree, and 40 degree prostatic urethra bends are shown in figure 3, 4, and 5, respectively.
The TRUS ultrasound image of the 20 degree urethra bend prostate phantom and 3D image of the prostate can be found in figure 6. Since the prostate size and shape is identical in all three phantoms only the 20 degree TRUS ultrasound image is shown. Since access to the MRI machine is not yet available a simple comparison between the SOLIDWORKS model of the prostate dimensions and the TUUS and TRUS images was done. The prostate dimensions measured from the SOLIDWORKS model are as follows, the anterior to posterior dimension is approximately 35mm and from left to right is approximately 51mm. When the prostate phantom is manufactured these dimensions will change be ± a few mm, but we will accept these dimensions for the time being. An initial estimate of the anterior to posterior (A-P) and left to right (L-R) dimensions of the prostate from the TUUS images are as follows, for the 20 degree phantom A-P = 36.60mm and L-R = 48.32mm, for the 30 degree phantom A-P = 36.21mm and L-R = 50.51mm, for the 40 degree phantom A-P = 36.07mm and L-R = 48.70mm. From the TUUS images for all three prostatic urethra bends the average percent difference in the A-P is 3.7% and in the L-R is -3.58%. For the TRUS images an initial estimate of the A-P and L-R dimensions of the prostate for the 20 degree prostatic urethra bend A-P = 25.27mm and L-R = 29.43mm, this is a -27.8% and -42.29% difference when compared with the dimensions measured from the SOLIDWORKS prostate model. This large discrepancy in the TRUS prostate dimension could be attributed to conversion between the number of pixels to mm. When the TRUS images were collected the saved images were not calibrated and I used the number of pixels to calculate the dimensions of the prostate. I believe that this can be resolved in the future by selecting the appropriate settings in the TRUS machine prior to collecting the data. This data shows that there is good agreement between the TUUS images and the SOLIDWORKS model. However, the calculated TRUS dimensions are suspect until more investigation is done to determine the real reason for the large discrepancy between the TRUS and SOLIDWORKS dimensions.

Challenges:
Some of the challenges that were encountered during this work are the stability of the phantoms over time, acquiring IVUS catheters, access to the imaging tools (TUUS imaging machine, TRUS imaging machine and MRI machine) needed for this research and scheduling time to use those tools. The tools needed to accomplish the research tasks outlined in the statement of work are used routinely for patients at UCLA Ronald Reagan hospital, which make it difficult to have physical access to the tools. Also at the beginning of this research period it took a considerable amount of time to get in contact with the appropriate persons to get permission to use the equipment and to develop a collaborative working relationship with the staff to get physical access to use the equipment. Now that a relationship has been established with the appropriate staff members to use the tools needed, I don't foresee any issues with having access to the imaging tools required for this project. In addition, it took a considerable amount of time to

acquire samples of the IVUS catheters needed to perform the *in vitro* experiments. Currently, enough IVUS catheters (Qty 3) have been acquired to perform the necessary *in vitro* experiments. The fabricated phantoms have a finite shelf life and after several weeks of storage the phantoms become unstable and degrade in size and elasticity. This requires scheduling time to use all three imaging machine within a short period of time which is challenging. Also the IVUS probes have a finite number of trials, usually about 5 trials per probe, this restricts the number of *in vitro* experiments that can be done, since I have a limited quantity of IVUS catheters. I plan on contacting GE to acquire samples of the IVUS probes to abate this issue.

IRB Approval for pilot Study

During this period an application titled "A study to determine accuracy of transurethral ultrasound (TUUS) imaging" was submitted to the UCLA institutional review board (IRB) for review. The application was approved by the UCLA IRB (IRB#15-000120). This will facilitate the accomplishment of the third aim of this project which is a pilot study to evaluate MR-TUUS fusion in brachytherapy needle placement.

c. **What opportunities for training and professional development has the project provided?**
   This project has provided the opportunity for IRB training, training on the use of the Volcano IVUS imaging machine, and training on the Artimus 3D TRUS machine.
d. **How were the results disseminated to communities of interest?**
   Nothing to Report
e. **What do you plan to do during the next reporting period to accomplish the goals?**
   Finish the TRUS and MRI imaging of the current prostate phantoms. Compare the volume reconstruction accuracy and registration error of 3D TUUS to 3D TRUS using the MRI image as the ground truth. Refine the 3D TUUS reconstruction code and perform another prostate phantom in vitro experiments with the additional variable of having three different prostate phantom size in this experiment.

4. **Impact**
   a. **What was the impact on the development of the principle discipline of the project?**
      Nothing to Report
   b. **What was the impact on other disciplines?**
      Nothing to Report
   c. **What was the impact on society beyond science and technology?**
      Nothing to Report

5. **Changes/Problems:**
   Nothing to Report

6. **Products:**

Nothing to Report

7. **Participants & Other Collaborating Organizations:**
   a. **What individuals have works on the project?**
      Name: Dr. George Saddik Ph.D.
      Project Role: PI
      Research Identifier: UCLA ID# 104243711
      Nearest person month worked: 12
      Contribution to Project: N/A
      Funding Support: N/A
   b. **Has there been a change in the active other support of the PD/PI(s) or senior /key personnel since the last reporting period?**
      Nothing to Report
   c. **What other organizations were involved as partners?**
      Nothing to Report

8. **Special Reporting Requirements:**
   Nothing to Report

9. **Appendices:**
   a. **References:**

      i. David R. Holmes III, Brian J. Davis, Christopher C. Goulet, Torrence M. Wilson, Lance A. Mynderse, Keith M. Furutani, Jon J. Camp, Richard A. Robb, Shape analysis of the prostate: Establishing imaging specifications for the design of a transurethral imaging device for prostate brachytherapy guidance, *Journal of Brachytherapy*, 13 (2014) 465-470.
      ii. M. O. Culjat, D. Goldenberg, P. Tewari, and R. S. Singh, "A Review of Tissue Substitutes for Ultrasound Imaging," *Ultrasound in Medicine & Biology*, vol. 36, pp. 861-873, 6// 2010.

   b. **Prostate Phantom Recipe**
      i. Prostate:
      3.5 g Agar in 100 mL water
      Pelvis:
      3.5 g Agar and 4.5 g glass microbeads in 100 mL of water